REMARKS

Claims 1-6 are presently under examination. Claims 7-32 are withdrawn as non-elected. Claims 1 and 4 are amended herein. The amendments add no new matter.

Title of the Application:

The Office Action states that a new title is required because the present title is directed to the crystal structure of ribosomal protein L11/GTPase activating region rRNA and uses thereof whereas in contrast the elected claims include a method for identifying a potential modulator of ribosomal protein L11 GAR activity.

Applicants submit that the amended title provided herein is sufficient to address this objection.

Claim Objections:

Claims 1 and 4 are objected to because the sub-headings "a," "b," etc. have periods after them. Applicants have amended the periods to ")"s.

Objection to the Specification:

The Office Action points out a misspelling on page 5, line 2. The misspelling of "embodiment" is corrected herein by amendment to the specification.

Claim Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 1-6 are rejected under 35 U.S.C. §112, first paragraph for lack of enablement. The Office Action states that "the specification, while being enabling for some modulators such as thiostrepton and micrococcin, does not reasonably provide enablement for where to obtain unspecified test compounds in a method for identifying a potential modulator." The Office Action states that "Although the said GTPase activating region (GAR) is defined within the atomic coordinates, the number of molecules that are known to scientists is enormous. A narrowing of the selection of test compounds is needed to practically focus in to a potential modulator of GAR activity in a reasonable amount of computation time." The Office Action concludes that the invention as presently stated in the claims does not include such narrowing

guidelines and causes a lack of scope of enablement of the instant invention for one skilled in the art." Applicants respectfully disagree.

Applicants submit that the specification teaches not only the selection of compounds from among chemical libraries, such as the Maybridge Chemical directory and other sources known to those skilled in the art (page 50, lines 18-22), but also rational design and synthesis of potential modulators. As such, Applicants submit that the specification provides ample guidance regarding how one of skill in the art would narrow the selection of test compounds without undue experimentation. This guidance is discussed below.

Applicants submit that the specification provides description of computer modeling and docking algorithms useful in the rational design and computational screening of molecules that will bind a target defined by three dimensional structure of the L11/GAR. Rational design is described, for example, at page 37, line 11 to page 44, line 16 and at page 55, line 12 to page 56, line 4. More specifically, the specification describes the analysis of binding surfaces of the L11/GAR, including factors to consider such as van der Waals contacts, electrostatic interactions and hydrogen bonding opportunities, stating that "this information is then used with computer simulation techniques to map the favorable interaction positions for functional groups such as protons, hydroxyl groups, amine groups, divalent cations, aromatic and aliphatic functional groups, acetamide, methanol, etc. These groups can be designed into a synthetic ligand" (page 38, lines 2-8). The specification further teaches that "the L11/GAR structure coordinates may be used to screen computationally small molecule data bases for chemical entities or compounds that may bind in whole, or in part, to the L11/GAR, to GAR, or to L11" (page 38, lines 9-11).

Computer program packages useful for both modeling the interaction regions of L11/GAR with candidate molecules and for rational design of candidate molecules are described at page 40, line 14, to page 42, line 14. More specifically, the specification states that

> "One skilled in the art may use one of several methods to screen chemical entities of fragments for their ability to associate with L11/GAR and more particularly with the individual binding domains comprising the L11/GAR active sites. This process may begin by visual inspection of, for example, the active site on the computer screen based on the L11/GAR RNA coordinates in Fig.7. Selected fragments or chemical entities may then be positioned in a variety of orientations,

> or "docked", within an individual binding target site of the L11/GAR as defined herein from analysis of the crystal structure data." (page 40, lines 14-20).

The specification also states that "Specialized computer programs may also *assist in the process of selecting fragments or chemical entities*" that can associate with binding domains in the active site(s) of the L11/GAR (page 41. lines 1-2; emphasis added), and then lists 6 computer programs, including GRID, MCSS, AUTODOCK, DOCK, CERIUS II and Flexx that can be used for this purpose. Thus, the specification teaches how to identify chemical entities that may bind to particular areas of the L11/GAR active sites identified in the crystal structure. The specification also describes examples of computer programs that facilitate *linking* such chemical entities together after they are identified. These programs are listed on page 42 and include CAVEAT, 3D database systems such as MACCS-3D, and HOOK. In view of this guidance and the abilities of one of skill in the art, Applicants submit that the specification provides disclosure necessary for one of skill in the art to identify chemical entities that may bind individual binding domains comprising the L11/GAR active sites, and to design candidate molecules that comprise these chemical entities linked together in a manner with the potential to bind the L11/GAR. Applicants submit that, in view of this rational design enabled by the specification and the L11/GAR crystal structure taught therein, one of skill in the art would be able to choose or design candidate molecules to test, either physically or by computer modeling, for binding to the L11/GAR.

In addition to teaching how to build a candidate modulator in the step-wise fashion discussed above, the specification also describes the "de novo" design of candidate modulators, using either an empty active site or optionally including some portion(s) of a known inhibitor(s). Such methods are described at page 42, , line 15 to page 43, line 4 and includes the use of computer programs such as LUDI, LEGEND and LeapFrog. In view of these teachings, Applicants submit that it is not necessary for the claims to be limited to a particular source or type of candidate molecules. One of skill in the art can, using the guidance provided in the specification, the crystal structure coordinates of the L11/GAR provided, and one or more of the molecular modeling programs described, design the necessary candidate molecules. It is within the abilities of one skilled in the art to *make* the designed candidate molecules, and it is within the abilities of one skilled in the art, following guidance in the specification, to test those

candidates using computer modeling, physical interaction studies, or both, to determine if a candidate binds the target.

In view of the above, Applicants submit that the specification is fully enabling for one of skill in the art to identify or rationally design a potential modulator without undue experimentation. Applicants respectfully request reconsideration and withdrawal of this §112, first paragraph rejection.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 1-6 are rejected as indefinite under 35 U.S.C. §112, second paragraph.

Claim 1 is rejected as indefinite for reciting the phrase "a method of identifying" in the preamble when the claim limitations do not actually include an identification step. Applicants submit that the amendment of claim 1 to recite "wherein a modulator of L11/GAR activity is identified" is sufficient to overcome this ground of rejection.

Claim 1 is also rejected for reciting the phrase "using a three-dimensional structure." The Office Action states that "the claimed method appears to be computer-implemented method (at least steps a-c, and possibly d, as well), so it is unclear how one of skill in the art would "use a three-dimensional structure" (a physical entity) in this method." Applicants respectfully disagree.

Applicants submit that the claim does not recite only a "three dimensional structure" but "a three dimensional structure of L11/GAR complex *as defined by atomic coordinates of the L11/GAR according to Table II"* (emphasis added). That is, the *structure* recited is that "defined by the atomic coordinates of the L11/GAR." The three dimensional structure defined by the atomic coordinates of the L11/GAR is a representation of the L11/GAR, and not a "physical entity" as suggested in the Office Action. Thus, Applicants submit that there is no lack of clarity in the phrase "using a three dimensional structure of L11/GAR complex as defined by atomic coordinates of the L11/GAR according to Table II." Applicants respectfully request reconsideration and withdrawal of the rejection.

Claim 1 is also rejected because the phrase "contacting said potential modulator" is said to be unclear. The Office Action states that "it is unclear if the claim limitation is supposed to be entirely computer-implemented (virtual step) or if the last step is laboratory based (physical step)." The Office Action states that if the claim limitation is intended to be a computer-implemented step then correction is suggested by substituting "contacting" for a term commonly used in the computer-related arts.

Applicants submit that the amendment herein of claim 1 to recite "wherein said contacting comprises contacting by computer modeling or by physically contacting said potential modulator with the L11/GAR" is sufficient to overcome this ground of rejection. Applicants submit that the specification makes it clear that the "contacting" step can be performed either virtually on the computer, or physically in the laboratory, or both – i.e., computer model contacting as an initial screen, followed by physical contacting to confirm binding by those compounds that pass the computer contacting test. For example, at page 40, the specification states:

> The potential modulating or binding effect of a chemical compound on the L11/GAR may be analyzed prior to its actual synthesis and testing by the use of *computer modeling techniques*. If the theoretical structure of the given compound suggests insufficient interaction and association between it and the L11/GAR, synthesis and testing of the compound is obviated. However, *if computer modeling indicates a strong interaction, the molecule may then be synthesized and tested for its ability to bind to the L11/GAR domain and to inhibit* using the assays described herein. In this manner, synthesis of inoperative compounds may be avoided. (Page 40, lines 2-9; emphasis added)

Thus, the language of the amendment is fully supported in the specification. in view of the amendment, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 1 and 4 are rejected as indefinite for recitation of the abbreviation "L11/GAR." The Office Action suggests adding the full name in parentheses. Applicants submit that the specification clearly defines the terms "GAR" (page 1, line 20, page 13, lines 1-13), and "L11/GAR" (page 13, line 14 to page 14, line 4). In view of these definitions, Applicants submit that there is no ambiguity as to what is meant by the term "L11/GAR." Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 1 is rejected as indefinite for recitation of "determine the ability [...] to modulate L11/GAR activity." The Office Action states that "it is unclear what criteria and to what extent the criteria must be met to qualify as having the ability to modulate activity." Applicants respectfully disagree.

Applicants submit that the term "L11/GAR activity" is defined in the specification as follows:

> "'L11/GAR activity' may include one or more of the following: movement of the N-terminal lobe of L11; binding or displacement of thiostrepton or micrococcin; RNA translation, translation elongation, inhibition of amino acid addition, GTPase activity, and/or inhibition of elongation factor G (EF-G)-dependent GTP hydrolysis." (page 14, lines 5-8)

Further, Applicants submit that the term "modulate" is defined at page 17, line 24 to page 18, line 1 in terms of an increase or decrease in some activity. The terms "increase" and "decrease" are also defined with respect to L11/GAR activity at page 18, lines 4-20, in terms of at least a 50% increase or decrease in either GTP hydrolysis (for determining increase or decrease) or translation activity (for determining decrease) in the presence of a modulator. As such, Applicants submit that it is clear what are the metes and bounds of the phrase "determine the ability of said potential modulator to modulate L11/GAR activity. Applicants respectfully request reconsideration and withdrawal of this rejection.

Claim 4 is rejected because the term "said compound" in line 2 lacks sufficient antecedent basis. The Office Action suggests amendment to "said potential modulator." Applicants have amended the claim as suggested.

Claim 4 is rejected for reciting the term "capable of associating," which the Office Action states is unclear as to "what criteria and to what extent the criteria must be met to be considered capable of associating with the L11/GAR." Applicants submit that the amendment of the cited language to recite instead "identifying chemical entities or fragments with the potential to bind said L11/GAR" is sufficient to overcome this rejection. The language of the amendment is supported in the specification where it states "The potential modulating or binding effect of a chemical compound on the L11/GAR may be analyzed prior to its actual synthesis and testing by the use of computer modeling techniques" (page 40, lines 2-4). The specification further states

that "One of skill in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with L11/GAR and more particularly with the individual binding domains comprising the L11/GAR active sites" (page 40, lines 14-16). The methods are then described over the following two pages. Applicants submit that one of skill in the art would know what is meant by "chemical entities or fragments with the potential to bind the L11/GAR" in terms of chemical entities or fragments identified by computer modeling programs. Given the coordinates of the L11/GAR target, the programs are designed to predict what chemical entities or fragments will bind the target or parts of the target. In view of this, Applicants respectfully request the withdrawal of this rejection.

Rejections under 35 U.S.C. §103(a):

Chen et al. in view of *In re Gulack*

Claims 1-6 are rejected as obvious under 35 U.S.C. §103(a) over Chen et al. (U.S. 6,160,092) in view of *In re Gulack* (703 F.2d 1381, 1385 (Fed. Cir. 1983)). The Office Action states that Chen et al. describe 1) "a method for identifying an agent that enhances or diminishes the activity of a protein," 2) "determining the three-dimensional structure of a compound based on structural coordinates obtained from X-ray crystallographic analysis of crystals," and 3) using computer modeling to select potential agents and contacting the agents with the protein. The Office Action states that "even though the method described by Chen et al. does not specify that the active site was identified by the crystal structure coordinates and the three dimensional model of the ribosomal protein L11/GAR RNA complex, the specific limitations of crystal structure coordinates and the three dimensional model of the L11 GAR complex in this instant case do not distinguish the invention from the prior art in terms of patentability, because they are non-functional descriptive matter."" The Office Action then cites *In re Gulack* as defining non-functional descriptive material to be descriptive material that is not functionally related to the substrate, in such a way that this descriptive material will not distinguish the invention from the prior art in terms of patentability. The Office Action cites the MPEP §2106, section VI as stating that "the descriptive material unable to exhibit any functional interrelationship with the way in which computing processes are performed does not constitute a statutory process, machine, manufacture or composition." The Office Action continues, stating "Due to the fact that the

coordinate data set derived from the crystal structure of the L11/GAR complex to develop three dimensional models in the instant case are merely stored so as to be read or outputted by a computer without creating any functional interrelationship, either as part of the stored data or as part of the computing processes performed by the computer, this descriptive material alone does not impart functionality either to the data as structured, or to the computer. Finally, the Office Action states "As the invention of Chen et al. contains a method for identifying agents that interact with a protein and various modifications to their invention would be apparent to a skilled artisan, a skilled artisan would have been motivated to include any crystalline protein already identified into this method in order to search for new drugs." The Office Action concludes that it would have been obvious to one of skill in the art at the time the invention was made to include the three-dimensional model of the L11/GAR complex in the method, in order to search for possible drug candidates as described by Chen et al. Applicants respectfully disagree.

First, Applicants submit that in order to render a claimed invention obvious, the cited references must teach or suggest all elements of the recited claim. Applicants submit that Chen et al. does not teach or suggest the atomic coordinates for the L11/GAR according to Table II of the instant specification as recited by claim 1. The teaching, by Chen et al., of the atomic coordinates of the STAT protein and their use in screening assays to identify modulators of STAT activity *in no way* teaches or suggests the atomic coordinates of the L11/GAR complex reported in the instant specification. That is, one of skill in the art, looking at the atomic coordinates of the STAT protein reported by Chen et al., would have absolutely no way of predicting what the coordinates of the L11/GAR would be. As such, the Chen et al. reference does not teach or suggest the "atomic coordinates of the L11/GAR according to Table II," and cannot render obvious the claimed invention.

Second, the reasoning of the Office Action is based on the incorrect presumption that the atomic coordinates of the L11/GAR were already known. That is, the Office Action stated "a skilled artisan would have been motivated to include *any crystalline protein already identified* into this method in order to search for new drugs." Applicants submit that the atomic coordinates for the L11/GAR were not available in the prior art, and thus were not "already identified" at the time of invention. Rather, the atomic coordinates for the L11/GAR are described for the first time in Table II of the instant specification, so any reasoning based on the

alleged obviousness of applying the methods taught by Chen et al. for the identification of compounds that modify STAT activity to L11/GAR atomic coordinates existing at the time of invention is incorrect.

Finally, Applicants respectfully disagree with the statement that the atomic coordinates are non-functional descriptive matter. Applicants submit that computer modeling programs require data, in the form of mathematical representations such as the atomic coordinates, in order to produce a model which can then be used in the design or prediction of interacting molecules. Without the mathematical representation of the macromolecule, the computer modeling programs are non-functional for this purpose. Thus, it makes no sense to refer to the coordinates as non-functional descriptive matter.

In view of the above, Applicants submit that claims 1-6 cannot be obvious over any interpretation of Chen et al. in view of *In re Gulack*. Applicants respectfully request the withdrawal of this §103(a) rejection of these claims.

Chen et al. in view of Hinck et al.

Claims 1-6 are rejected as obvious under 35 U.S.C. §103(a) over Chen et al. in view of Hinck et al. (1997, J. Mol. Biol. 274: 101-113) and *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594). Chen is cited as above. The Office Action states that Chen et al. do not describe the three dimensional structure of the L11/GAR complex. The Office Action states that "Hinck et al. describe a three-dimensional structure of the RNA binding domain of ribosomal protein L11 as determined by NMR (abstract)," and that although Hinck et al. do not describe the atomic coordinates of the L11/GAR according to Table II, as states in claim 1, this limitation appears to be merely an additional measurement of the same L11/RNA complex as described by Hinck et al." The Office Action then cites *In re Best* and *In re Fitzgerald* to support "rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed." The Office Action states that "in such a situation the burden is shifted to the applicants to prove that subject matter shown to be in the prior art does not possess characteristic relied on." Finally, the Office Action states that "a skilled artisan would have been motivated to include any crystalline protein complex already identified into this method in order to search for new

modulators," and that it would have been obvious "to include the three dimensional model of the L11/GAR complex (as stated by Hinck et al.) in the method, in order to search for possible drug candidates, as described by Chen et al." Applicants respectfully disagree.

As noted above, Applicants submit that the atomic coordinates of the L11/GAR were not known in the art at the time of the claimed invention. Further, Applicants respectfully submit that the assertion that the atomic coordinates of the L11/GAR are inherent in the NMR structure is incorrect. First, the crystal structure is of much higher resolution, literally at the atomic level, than is the NMR structure of a given complex. That is, one of skill in the art cannot deduce the atomic coordinates of a macromolecule from the structural representation provided by NMR. If this were true, there would be no need to expend the considerable effort necessary to determine crystal structures where NMR structures are available. Under the law regarding inherency, in order for a non-disclosed, but "inherent" property in a reference to satisfy a claim limitation and thereby render the reference anticipatory of the claim as a whole, the property "must be necessarily present and a person of ordinary skill in the art would recognize its presence." Crown Operations International Ltd. v. Solutia Inc., 62 USPQ2d 1917, 1923 (U.S. Fed. Cir. 2002). Applicants submit that because one of skill in the art cannot deduce those atomic coordinates from the structural representation provided by NMR, a person of ordinary skill in the art would not recognize the presence of the atomic coordinates in an NMR structure representation. As such, the atomic coordinates are not an inherent property of the NMR structural representation. Such coordinates cannot be determined without crystallizing the macromolecule, in this case, L11/GAR.

In view of the above, Applicants submit that Chen et al. does not teach the atomic coordinates of the L11/GAR as provided in Table II of the specification, as recited by the claims, and that Hinck et al. does not remedy this deficiency of Chen et al. by merely reporting NMR structure. Therefore, Applicants submit that the invention of claims 1-6 cannot be obvious over any combination of Hinck et al. and Chen et al. Applicants respectfully request reconsideration and withdrawal of this §103 rejection.

In view of the above, Applicants submit that all issues raised in the Office Action have been addressed herein. Reconsideration of the claims is respectfully requested.

Respectfully submitted,

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